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APR 10 2007

Application No. 10/005,438  
Response to Jan 10, 2007 Office Action  
Page 4 of 8

**REMARKS**

Claims 14-22 are currently pending. Applicants have amended claim 14 to more particularly and distinctly claim that which Applicants regard as their invention. No new matter has been introduced by this amendment.

**I. Claim Objections**

Claim 19 has been objected to for including a withdrawn claim. Applicants request that this rejection be held in abeyance until allowable subject matter is determined.

**II. Rejection Under 35 U.S.C. § 112, Second Paragraph**

Claim 14 has been rejected as being indefinite because it recites SEQ ID NO 1. Applicants have amended claim 14 to correct the typographical error. The claim now refers to the amino acid sequence of SEQ ID NO 2.

In view of this amendment, Applicants request that the rejection be withdrawn.

**III. Rejection Under 35 U.S.C. § 103**

A. Claims 14 and 18-19 have been rejected as unpatentable over Landolphi (U.S. Pat. No. 5,349,053), in view of Frincke (EP 467,416) in further view of Blatt (U.S. Pat. No. 5,373,808). The Office contends that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include interferon-alpha (a species of the generic ligand of lymphokines) because Landolphi teaches that virtually any naturally-occurring ligand, or portion thereof, capable of binding to a receptor may be used as the ligand, including growth factors, lymphokines, peptide hormones, lectins, and adhesion molecules (column 4, line 56+)" (Office Action at page 6). Applicants respectfully traverse this rejection.

As presented in the Appeal Brief, there are three arguments that the Office has still not addressed.

The first issue has to do with the requirement that the reference be enabling. Before a reference can even be considered to constitute legally cognizable prior art, it must teach how to make what it discloses. *In re Hoeksema*, 399 F.2d 269, 274, 158 U.S.P.Q. 596, 600-01 (C.C.P.A. 1968) held that the "true test of any prior art relied on to show or suggest that a chemical compound is old, is whether the prior art is such as to

Application No. 10/005,438  
Response to Jan 10, 2007 Office Action  
Page 5 of 8

place the disclosed 'compound' in the *possession of the public*" (emphasis added). The test whether a particular compound described in the prior art may be relied upon to show obviousness is whether the prior art provided an enabling disclosure with respect to the disclosed compound. *Ashland Oil, Inc. v. Delta Resins Refractones* 776 F2d. 281, 227 USPQ 657 (Fed. Cir. 1985). Because the evidence in *Ashland* showed that a certain compound was a "hypothetical structure", the court found it was not persuasive of obviousness.

In this case, the Office has admitted that Landolphi does not disclose interferon. The Landolphi patent merely lists lymphokines as possible ligands, with no specific reference to interferons, thus these are merely hypothetical structures with no enabling disclosure. As further evidence of the fact that the Landolphi patent does not enable embodiments other than IL-2, excerpts from the prosecution history of the Landolphi patent were presented to the Examiner in the Response filed on April 25, 2005. These excerpts are provided for the Appeal Bd.'s convenience in Exhibit C. In the prosecution history of the Landolphi patent, the Examiner stated at page 5 of the Office Action dated March 23, 1992, (See Exhibit C):

[P]age 7 merely list[s] several lymphokines and growth factors that can be used as the ligand. . . . [T]he specification is non-enabling for the preparation of immunoligands broadly, nor is it evident that the scope of these immunoligand[s] would have a utility and possess the desired physical and functional properties for each portion of the immunoligand. Lymphokine (LK) is generic, and represent[s] a broad and diverse group of proteins that are functionally and patentably distinct, such that the preparation of an immunoligand with one LK such as IL-2 cannot effectively predict or enable the preparation and usefulness of the entire scope of LK. (emphasis added)

Applicants of the Landolphi patent were unable to rebut this rejection and ultimately had to narrow their claims to the immunoligand IL-2. (See Exhibits C). Thus, the Landolphi patent fails to provide the necessary teachings to put the public in possession of the full scope of the invention as disclosed and as such cannot constitute legally cognizable prior art for the presently claimed invention.

The Office has still not addressed this argument.

Application No. 10/005,438  
Response to Jan 10, 2007 Office Action  
Page 6 of 8

The second issue is the lack of motivation to combine references. In the present case, there is no suggestion or incentive to combine the references cited by the Office, and there is no reasonable expectation of success.

Using an applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of § 103 of judging obviousness at the point in time when the invention was made. See *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988). Moreover, where the prior art has not recognized the "result-effective" capability of a particular invention parameter, no expectation would exist that optimizing the parameter would successfully yield the desired improvement.

Here, the Office has pieced together disparate references using the Applicants' specification as a guide. Landolphi discloses chimeric molecules that "exhibit the high degree of specificity associated with the ligand yet retain various effector functions characteristic of immunoglobulin heavy chains." (Abstract) These effector functions include fixing complement and/or mediating antibody dependent complement fixation. (Col. 2, lines 50-53.) The problem to be solved by Landolphi was "the need for increasing the specificity and improving binding affinity of immunoglobulins beyond the immunoglobulin gene superfamily, while retaining their useful characteristics." (Col. 2, lines 30-33.) The purpose was not related to increasing the serum half-life of the hybrid molecule. The IL-2 construct and experiments disclosed further that end. Therefore, the motivation to combine the Landolphi reference with the Frinke reference is not present.

Moreover, the Frinke reference does not teach fusion proteins. Frinke teaches creating antigen-antibody complexes between a given protein and an antibody that binds to that protein. This is a totally different mechanism of extending half-life and does not provide a motivation to combine this reference with Landolphi in the absence of Appellant's specification. Even assuming that this reference was considered, the attachment of the antibody to the antigen protein is through its **Variable** region, not the Fc constant region. There is no suggestion that using the construct of Landolphi would accomplish the same thing as the Ag-Ab complex taught by the '416 patent because they are two different approaches. The Office has not addressed the fact that a skilled

Application No. 10/005,438  
Response to Jan 10, 2007 Office Action  
Page 7 of 8

artisan reading the disclosure of Landolphi which is directed to improving binding affinity and specificity, would look to Frinke directed to Ag-Ab complexes that bind the variable region to solve the problem of the present invention.

Thus, the Office has not addressed this argument either.

Finally, the third issue is unexpected results. Regardless of the case for obviousness, if Applicants demonstrate unexpected results over the prior art, the invention is non-obvious. Again the Office has never addressed the Applicants' argument of unexpected results. Appellants also presented evidence of unexpected results in the Response filed on March 14, 2006, which was improperly considered by the Office.

Appellants cited to the specification at Example 1, paragraph [0025] (Exhibit B) as further evidence of nonobviousness. The *in vivo* pharmacokinetic studies in primates resulted in a 40-fold longer serum half-life than unmodified interferon. The clearance half-life after subcutaneous injection was almost 120 fold longer.

The Frinke reference (EP467416) only reported a 12-fold increase in half-life (col. 6, lines 53-57.) Since the Landolphi patent only constructed IL-2-Ig complexes, and does not disclose any increases in half-life because that was not the intended purpose of the Landolphi invention, the present invention clearly demonstrates unexpected results over this patent as well. Peterhans discloses labeled constructs for an entirely different purpose, thus no disclosure of increased half-life.

Clearly, a 40-fold increase in serum half-life of the claimed interferon-Fc hybrid molecule over interferon alone and a 120-fold longer clearance half-life is unexpected over the teachings of Frinke of 12-fold.

Therefore, the Office has not established a *prima facie* case of non-obviousness, and the rejection should be withdrawn.

**B.** Claim 15 has been rejected as unpatentable over Landolphi (U.S. Pat. No. 5,349,053) and Frinke (EP 467,416) in view of Blatt (U.S. Pat. No. 5,373,808), and further in view of Capon et al (U.S. Pat. No. 5,116,964).

Application No. 10/005,438  
Response to Jan 10, 2007 Office Action  
Page 8 of 8

In view of the arguments presented above, the Office has not established a prima facie case of obviousness for the primary reference. Therefore, this rejection should also be withdrawn.

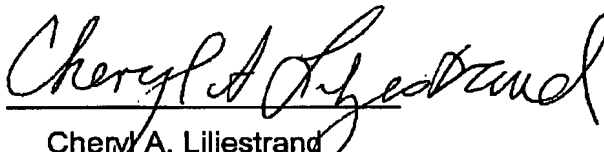
C. Claim 16 has been rejected as unpatentable over Landolphi (U.S. Pat. No. 5,349,053) and Frincke (EP 467,416) in view of Blatt (U.S. Pat. No. 5,373,808), and further in view of Freeman et al (U.S. Pat. No. 6,130,316).

In view of the arguments presented above, the Office has not established a prima facie case of obviousness for the primary reference. Therefore, this rejection should also be withdrawn.

#### **Conclusion**

In view of the previous remarks, Applicants submit that the claims are in condition for allowance and request rejoinder of claims 17, 20-22.

Respectfully Submitted

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